In the Specification:

Please amend the specification as follows:

On page 1, after the title, insert the following sub-heading:

--Field of the Invention--

On page 1, after the first full paragraph, insert the following sub-heading:

--Background of the Invention--

On page 2, the second full paragraph has been amended as follows:

It has been found that the abovementioned requirements for sample preparation are met by a miniaturized analytical unit consisting of a microstructured planar channel system made of plastic as ~~continuous-flow~~ flow through unit, an adaptor chamber for reversibly receiving the ~~continuous-flow~~ flow though unit, a fluidics supply, a power supply and detectors. The inventive analytical unit in particular has an apparatus for precise delivery of large sample volumes above 0.1 µl and preferably an apparatus for discharging sample volumes. Separation is preferably performed isotachophoretically.

On page 2, after the first full paragraph, insert the following sub-heading:

--Summary of the Invention--

On page 3, the first full paragraph has been amended as follows:

The present invention therefore relates to an analytical unit for sample preparation at least comprising a ~~continuous-flow~~ flow through unit made of plastic having a microstructured channel system, an adaptor chamber for reversibly receiving the ~~continuous-flow~~ flow through unit, a fluidics supply, a power supply and at least one detector, characterized in that to receive the sample a channel section is provided at the ends of which in each case are situated fluidic connections.

On page 3, after the fifth full paragraph, insert the following sub-heading:

--Brief Description of the Drawings--

On page 3, the seventh full paragraph has been amended as follows:

Figure ~~2~~ 2A shows a ~~possible~~ procedure in the charging of a miniaturized analytical unit.

On page 3, after the seventh full paragraph, insert the following paragraph:

Figure 2B shows an alternative procedure to Figure 2A,

On page 4, the second full paragraph has been amended as follows:

Figure ~~4~~ 4A illustrates a first approach to the discharge of a substance using the inventive discharge apparatus.

On page 4, after the second full paragraph, insert the following two paragraphs:

Figure 4B illustrates a second approach to the discharge of a substance using the inventive discharge apparatus.

Figure 4C illustrates a third approach to the discharge of a substance using the inventive discharge apparatus.

On page 4, paragraph 5 has been amended as follows:

~~The explanations to Figures 7 to 10 are found in Examples 3 and 4.~~ Figure 7 is a graph showing separation of cations from serum with time plotted on the X-axis and resistance on the Y-axis.

On page 4, before the sixth full paragraph, insert the following sub-heading:

--Detailed Description--

On page 4, after paragraph 5, insert the following paragraphs:

Figure 8 is a graph showing separation of components in a wine sample with time plotted on the X-axis and resistance on the Y-axis.

Figure 9 is a graph showing separation of a white wine sample with time plotted on the X-axis an resistance on the Y-axis.

Figure 10 is a graph plotting separation of a red wine sample with time plotted on the X-axis and resistance on the Y-axis.

The last paragraph bridging pages 4 and 5 has been amended as follows:

The inventive analytical unit for sample preparation consists at least of the following constituents:

- a ~~continuous-flow~~ flow though unit made of plastic having a microstructured channel system
- an adaptor chamber for reversibly receiving the ~~continuous-flow~~ flow through unit
- a fluidics supply
- a power supply
- at least one detector

The ~~continuous-flow~~ flow through unit is, in addition, structured so that an apparatus for delivering sample volumes between 0.1 µl and, depending on the system, typically 20 µl with a deviation of less than 5% is present. If the remaining instrument parameters of the analytical unit, for example the power supply, which are of importance for effective separation and analysis, are adapted appropriately, even greater sample volumes can be delivered. The sample volume is defined only by the volume of the channel section which is limited by the fluidics connections. Preferably, in addition, an apparatus for discharging sample volumes is integrated.

On page 5, the second full paragraph has been amended as follows:

The core of microfluidic or microstructured systems is generally a ~~continuous-flow~~ flow through unit which has at least the channel system and optionally recesses for integrating peripheral devices, and peripheral devices, such as detectors, fluidics connections, reservoirs, reaction chambers, pumps, control apparatuses etc. which can be integrated into the ~~continuous-flow~~ flow through unit or connected thereto. Suitable ~~continuous-flow~~ flow through units for an analytical unit are according to the invention systems in which, by joining together at least two components, for example substrate and cover, microchannel structures are produced which can be sealed liquid-tightly and/or gas-tightly.

On page 5, the third full paragraph has been amended as follows:

The channel system of the ~~continuous-flow~~ flow through unit typically has two or more channel segments for receiving separation buffers. These channel segments are each provided with fluidics connections for introducing and removing the buffers. If the channel segments additionally serve as separation channel, the fluidics connections can also be utilized for removing analytes or matrix components.

On page 6, the first full paragraph has been amended as follows:

Preferably, using the inventive analytical unit, the samples are fractionated isotachophoretically, since this gives the possibility of enriching very small amounts of analytes from large sample volumes and separating them. For this, the ~~continuous-flow~~ flow through unit must permit the sample volume to be introduced at the start of the isotachophoretic separation directly between two zones of aqueous buffers, in which case one buffer, the leading buffer, has ions of higher electrophoretic mobility than the sample components to be analysed and the other buffer, the terminating buffer, has ions of lower electrophoretic mobility.

On page 6, the second full paragraph has been amended as follows:

The components of the ~~continuous-flow~~ flow through unit of the analytical unit preferably consist of commercially available thermoplastics, such as PMMA (polymethyl methyacrylate), PC (polycarbonate), polystyrene or PMP (polymethylpentene), cycloolefinic copolymers or thermosetting plastics, for example epoxy resins. Preferably, all components of the system consist of the same material.

The last paragraph bridging pages 6 and 7 has been amended as follows:

For the integration of electrodes into the ~~continuous-flow~~ flow through unit, the electrodes are preferably mounted on a component of the system, the cover. For this purpose they must have an adequate adhesion strength on the plastic component. This is of importance both for joining together the individual components and for the later use of the entire apparatus. If adhesives, for example, are used during the joining of the components, the adhesive must not detach the electrode from the plastic surface. In addition, the electrodes should consist of chemically inert materials, for example noble metals (platinum, gold).

The first paragraph bridging pages 10 and 11 has been amended as follows:

After production and preparation of individual components, these are joined together. Preferably, one component, the substrate, is microstructured and provided with rear-side bore holes or recesses for filling the channels and/or contacting the electrodes. In addition, the use of a so-called sealing lip, that is to say an elevation on the substrates which completely encloses the channel structures with a height between typically 0.5 and 5 μm, has proved to be highly advantageous with respect to the adhesion process. The other component, the cover, serves for covering and, for example, is provided with the electrodes in the case of electrophoretic analytical units. In this case the cover according to the invention is termed electrode cover. For certain applications, the ~~continuous-flow~~ flow through units can require a functionalization of the component deviating from this preferred arrangement. In

this case, for example, more than two components, for example two covers and one substrate etc., can be joined together in order to generate channel structures which lie one above the other, or other functionalities, such as detection systems, reaction chambers etc., can be integrated into the components. According to the invention, all parts of the ~~continuous-flow~~ flow through unit which are joined together using a bonding process are termed components. They can be microstructured, provided with electrodes or have other functionalities. A subdivision of the components into substrates and covers or electrode covers, if the respective component is provided with electrodes, only serves for the more detailed description of the embodiment of the specific components and does not represent any restriction with respect to other properties of the components, such as microstructuring etc., or their combinations with one another.

On page 16, the second full paragraph has been amended as follows:

Preferably a ~~continuous-flow~~ flow through unit has a plurality of segments of separation channels in a series arrangement or in a branched arrangement. The segments have a relatively high cross-sectional area of typically 0.01 to 1.0 mm^2. Between the segments are constriction points having cross-sectional areas < 0.01 mm^2, which can optionally be provided with a detector during fabrication. In this manner it is possible to fabricate ~~continuous-flow~~ flow through units having differing volume ratios of separation channel to primary sample (corresponds to channel segment to sample delivery) by varying the position of the detector using one construction pattern for the capillary structure. The range of the volumetric ratio of separation channel/primary sample extends typically from 2/1 to 30/1. For small volumetric ratios, separation with low resolution in a short time is possible, in the case of high volumetric ratios, separation with high resolution for a longer separation time can be carried out.

On page 16, the third full paragraph has been amended as follows:

This apparatus is produced by the design of the channel system of the ~~continuous-flow~~ flow through unit and integration of fluidics connections.

On page 17, the fourth full paragraph has been amended as follows:

These apparatuses can be mounted preferably externally, as close as possible to the ~~continuous-flow~~ flow through unit.

On page 18, the second full paragraph has been amended as follows:

This type of filling avoids the disadvantages of electroosmotic injection, that is to say filling is largely independent of sample composition, pH and material of the ~~continuous-flow~~ flow through unit. The valves or tightly sealing pumps present prevent any interfering liquid motion, for example due to hydrostatic pressure differences or electroosmosis.

The last paragraph bridging pages 18 and 19 has been amended as follows:

The inventive apparatus has broad system-related limits with respect to the delivery volume. The volume of sample liquid which can be injected is determined solely by the volume of the channel section which is situated between the openings. By varying the geometric dimensions of this section in the design of the channel system of the ~~continuous-flow~~ flow through unit, sample volumes matched to the analytical problem can be established in advance. Similarly, it is possible to implement differently sized sections in parallel and/or in series, so that the volume of the section to be displaced by the sample solution can be varied. Preferably, therefore, a system for using the inventive apparatus is provided with a plurality of channel sections of different dimensions which can be used for sample delivery via respectively independent fluidic connections. As a result, sample volumes between 0.1 and 20 µl at differing levels, according to requirements, can be injected. In this case, usually coefficients of variation during delivery of sample volumes from 1 µl of about 5%, typically less than 2%, are achieved.

On page 19, the second full paragraph has been amended as follows:

Figure 1 shows by way of example a possible arrangement of the channel system of the inventive delivery apparatus. The channel system is subdivided into two channel sections 1A and 1B of differing volumes. Adjacent thereto is the separation channel 1C. Via the fluidic connections 11, 12 and 13, either channel section 1A (when connections 11 and 12 are open) or channel section 1B (during filling via connections 12 and 13) or the two channel sections together (during filling via connections 11 and 13) can be filled with the sample solution. After charging the delivery sections, by applying a voltage the sample in section 1C is separated. If only section 1A was filled with the sample, section 1B can also be used as a separation section, so that the separation section can be lengthened as required.

On page 20, the first full paragraph has been amended as follows:

To achieve the desired arrangement of sample and buffers in the channel system, firstly, as shown diagrammatically under Fig. 4A. The ~~A in the figure, the~~ fluidic connections F2 (outlet), F4, F5 and F6 (inlets) are opened and the channel system is filled via the three reservoirs with the two leading buffers (via R2 and R3, shown with diagonal lines or dots) and the terminating buffer (via R1, shown with vertical stripes). Excess buffer can exit via the fluidic connection F2. In this manner channel section K1 fills with terminating buffer, section K3 with leading buffer (LE2) via R2, section K4 with leading buffer (LE1) via R3 and channel section K2 contains a mixture of the two leading buffers. The fluidic connections F1 and F3 remain closed during this step.

The last paragraph bridging pages 20 and 21 has been amended as follows:

~~Part B of the figure~~ Fig. 2B shows how the sample is introduced into the channel section K1 and channel section K2 is filled via R3 with a leading buffer. The fluidic connections F5 and F6 are closed and no further terminating buffer is pumped via R1 and no further leading buffer (LE2) via R2. Fluidic connection F4 is open and channel section K2 is filled with leading buffer (LE1) via R3.

At the same time, the fluidic connection F1 is open and the sample is fed via F1 (shown as wavy lines). Excess sample and excess leading buffer (LE1) can exit via the open fluidic connection F2. By pumping the leading buffer (LE1) and the sample volume simultaneously against one another, a particularly precise filling of channel sections K1 and K2 is achieved. In this manner it is also possible to perform an exact charging using pumps which have low pulsation.

On page 22, the sixth full paragraph has been amended as follows:

Figure 3 shows diagrammatically the channel system of a ~~continuous-flow~~ flow through unit having an inventive apparatus for sample delivery and various possibilities for sample removal. The sections and segments of the channel system are labelled K1 to K7, the fluidic connections are labelled F1 to F8 and the detector electrodes D1. The system shown offers the possibility of purifying analytes by

1. the analyte not being moved and the matrix being removed
2. the analyte being removed.

On page 23, the fifth full paragraph has been amended as follows:

F5: Fluidic connection for charging the ~~continuous-flow~~ flow through unit with primary sample (outlet)

On page 24, the first full paragraph has been amended as follows:

For the inventive discharge apparatus, the ~~continuous-flow~~ flow through unit channel system must have, in addition to regions for sample delivery and a separation channel, at least one X- or Y-branch departing from a separation channel. For the integration of a plurality of discharge apparatuses, further branches can be introduced at any desired points of the channel system.

The last paragraph bridging pages 25 and 26 has been amended as follows:

According to the invention, all valves, pumps or micropumps, tightly closing micropumps,

micromixers or other connections of the inventive apparatus which serve for charging the channel system or for removing gas and liquid residues are termed fluidic connections. Generally, according to the invention the fluidic connections are not integrated into the ~~continuous-flow~~ flow through unit, but are connected to the ~~continuous-flow~~ flow through unit for use externally, that is to say from the adaptor chamber. In this manner, in the ~~continuous-flow~~ flow through unit, only appropriate openings need to be provided, which, in particular for ~~continuous-flow~~ flow through units which are replaced after use, is considerably more less expensive than the inclusion of expensive valves etc.

On page 26, the first full paragraph has been amended as follows:

Two essential requirements must be made of the hydro-dynamic reagent feed and primary sample feed:

1. At the start of the electrophoretic separation, within the ~~continuous-flow~~ flow through unit channel system, the zones of the buffer and of the sample liquid must be reproducibly situated at the positions which are predetermined by the geometry of the ~~continuous-flow~~ flow through unit.

The last paragraph bridging pages 26 and 27 has been amended as follows:

For point 1 it is necessary to remove any gas bubbles present from the channel system. This is readily possible using an active hydrodynamic system, for example a peristaltic pump, by using a gas bolus for collecting smaller gas bubbles. Owing to the volumes which are predetermined by the geometry of the ~~continuous-flow~~ flow through unit and mixing effects which are negligible in the region of the miniaturized dimensions, it is not necessary to perform precise volumetric metering. The pulsing of the liquid column which accompanies the operation of peristaltic pumps has been found not to be harmful provided that two pumps are in used in synchrony in countercurrent to one another. Similarly, the measurement principle is largely insensitive to variations in flow rates. This permits the use of robust and inexpensive apparatuses, for example peristaltic pumps, syringes or syringe pumps. The use of expensive and fault-susceptible so-called micropumps is not necessary.

On page 27, the first full paragraph has been amended as follows:

For point 2 it is necessary that the ~~continuous-flow~~ flow through unit channel system is hydrodynamically closed during electrophoresis. This is achieved either by pumps having an inherent valve function or by combining pumps with additional valves. The dead volume of the valves used has surprisingly been found not to be harmful provided that closing the valves was carried out synchronized in time.

On page 27, the third full paragraph has been amended as follows:

The power supply serves for carrying out the electrophoretic separation. It is implemented by connecting power electrodes to the ~~continuous-flow~~ flow through unit or, preferably, by contacting power electrodes integrated in the ~~continuous-flow~~ flow through unit via corresponding connections. Preferably, the apparatus for power supply delivers currents between 0 and 50 μA at a maximum voltage of 8 kV. The fluctuation in voltage should not be greater than ± 2%.

On page 28, the first full paragraph has been amended as follows:

The analytes are preferably detected optically or electrochemically. Generally, the detectors of the inventive analytical unit are arranged such that appropriate contact points are situated on the ~~continuous-flow~~ flow through unit which can then be connected externally, that is to say generally from the adaptor chamber. In the event of electric detection, therefore, in the ~~continuous-flow~~ flow through unit there are situated either integrated electrodes which can be contacted externally, or recesses into which electrodes can be reversibly introduced from the outside. The same applies to optical detectors.

The last paragraph bridging pages 30 and 31 has been amended as follows:

The adaptor chamber typically has an apparatus for holding the ~~continuous-flow~~ flow through unit. In addition, it serves for the reversible connection of fluidics, electrics, electronics and optical

connections. In this manner, the ~~continuous-flow~~ flow through unit can contain as far as possible only the channel system and necessary recesses for connecting fluidics, electrics etc. All further functionalities are provided by the adaptor chamber and can, if required, be connected to the ~~continuous-flow~~ flow through unit. Thus the ~~continuous-flow~~ flow through unit can be replaced as frequently as desired or can be changed with respect to the design of the channel structure and optional other functions, such as specific detectors, reaction chambers etc. can be changed without the adaptor chamber having to be changed greatly. The adaptor chamber thus contains, for example, a selection of the following functionalities: reversible connections of the power electrodes with the power supply, reversible connection of the detection electrodes with the measuring instrument for electrical conductivity, inlet and outlet capillaries for separation buffer and sample material, connections for invasive detectors (potentiometric or amperometric detectors, fibre-optic guides for measurement of transmitted light, scattered light or fluorescence etc.), outgoing capillaries for discharging separated-off components, cooling apparatus for removing Joule heat during electrophoresis, device for monitoring atmospheric humidity and dust particle density in the surroundings of the ~~continuous-flow~~ flow through unit.

On page 31, the first full paragraph has been amended as follows:

Functionalities are typically connected to the ~~continuous-flow~~ flow through unit via a holder integrated into the adaptor chamber, generally in the form of a plate. On this holder are situated, at positions which correspond to appropriate recesses in the ~~continuous-flow~~ flow through unit, matching connection elements. According to the invention connection elements are connections which ensure connection between the ~~continuous-flow~~ flow through unit and the functionalities in the adaptor chamber. The force which is necessary for sealing between the connection elements and the openings on the ~~continuous-flow~~ flow through unit is preferably provided via a press-on plate which presses the holder containing the connection elements onto the ~~continuous-flow~~ flow through unit. The connection elements are preferably supplied from the rear side of the holder via feed lines.

On page 31, the second full paragraph has been amended as follows:

In another preferred embodiment, the connection elements are not fixed in precise positions in a holder, but can be connected via variable tubings or telescope arms to any desired position in the ~~continuous-flow~~ flow through unit. In this case, each connection must be sealed individually, for example, via clamps etc. This embodiment permits a greater variability with respect to the ~~continuous-flow~~ flow through unit design, but requires greater effort during its connection.

The last paragraph bridging pages 31 and 32 has been amended as follows:

In a particularly preferred embodiment, therefore, the power electrodes and detection electrodes are connected to the power supply and the conductivity detector via telescopic electrodes which are mounted on one side of the holder. The fluidic connections, in contrast, are mounted on the holder in precise positions corresponding to the ~~continuous-flow~~ flow through unit. If a ~~continuous-flow~~ flow through unit with altered capillary geometry is to be used, the holder must be exchanged for a holder having correspondingly positioned fluidic connections.

On page 32, the first full paragraph has been amended as follows:

Figure 6 shows diagrammatically the connection of fluidics and electrics to a ~~continuous-flow~~ flow through unit. The ~~continuous-flow~~ flow through unit consists of a substrate (1) and a cover (2). The substrate (1) is microstructured, so that the channel system (3) is formed. On the cover (2) is applied a power electrode or detection electrode (4). The ~~continuous-flow~~ flow through unit is held by a holding apparatus (5). Above the continuous-flow unit is the holder (6) containing the connection elements, a fluidics connection (8a-8c) and an electrode connection (9a-9c). The fluidics connection is here additionally held via an exchangeable sealing plate (7) having contact elements. The fluidics connection essentially consists of a tube connection (8a) having a press-on screw for fastening and sealing the feeding capillary, a sealing element (8b) and a further sealing element (8c) which can be introduced as an exact fit into the recess in the substrate (1) and thus effects the connection between

the fluidic connection and the channel structure. The electrode connection essentially consists of an electrical contact for high voltage or for detection (9a), a spring (9b) and a contact part (9c) which can be brought into contact with the electrode (4) by the spring.

On page 33, the first full paragraph has been amended as follows:

The inventive analytical unit, by the combination of the inventive sample delivery, the possibility of integrating electrodes at any desired position of the ~~continuous-flow~~ flow through unit and the inventive discharge apparatus, makes it possible to carry out the most varied types of separations and analyses. Since very high sample volumes can be delivered, the analytical unit is suitable, in particular, for sample preparation. For example, the following separation problems and analytical problems can be dealt with:

1. Depletion of matrix components from a primary sample, preferably if the primary sample has a significant content of ionic matrix components which have a higher electrophoretic mobility than the analyte.

The last paragraph bridging pages 33 and 34 has been amended as follows:

One example of this is the removal of alkali metal cations from serum, plasma or whole blood (see Example 3). In this example, it must be ensured that dilution of the extracted electrolytes does not occur in the secondary sample. The ~~continuous-flow~~ flow through unit, because of the matrix residues remaining after the extraction must either be exchanged or purified.

On page 35, the first full paragraph has been amended as follows:

Preferably, the inventive analytical unit is used in such a manner that series of sample feeds following each other in time can be carried out without replacing reagents or the ~~continuous-flow~~ flow through unit. After completion of the series, the reagents and the ~~continuous-flow~~ flow through

unit can be replaced in a simple manner. A great advantage of the invention is that the analytical performance of the sample preparation is repeatedly available over a long period without maintenance expenditure and the place and time point of the analytical use can be selected in a broad range. In a preferred embodiment, the inventive analytical unit combines the advantages of a software-monitored complete system: standardizability of sample preparation, repeatability of separation, quality control, intrinsic error detection, with the advantages of miniaturization, such as low instrument costs, mobility, small size, low operating costs and simple operation.